Remarks

Objection to specification

The Examiner notes that the application contains two examples designated "Example 9." The Applicants appreciate the Examiner's notification of this typographical error and have amended the specification, changing the number of the second example designated "Example 9" to the appropriate sequential number.

Related to the typographical error of the preceding paragraph, the table in the mislabeled example is also mislabeled. Thus, the table in Example 13, presently labeled Table IX, has been amended to the appropriate sequential number, Table XIII.

Reply Under 37 C.F.R. § 1.111

I. Status of the Claims

Claims 92-103 are pending in this application. The Applicants thank the Examiner for renumbering the claims in accordance with Rule 1.126. All claims are rejected.

II. Rejection of Claims 92-95 under 35 U.S.C. § 103(a)

A. The Rejections

The Examiner rejected Claims 92-95 under 35 U.S.C. § 103(a) as unpatentable over De Meere, *et al.* (US Patent No. 5,384,132; "De Meere") in view of Buch-Rasmussen, *et al.* (US Patent No. 5,945,187; "Buch-Rasmussen") and Bornstein, *et al.* (US Patent No. 5,681,822; "Bornstein"). The Examiner alleges that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of various concentrations of recombinant human follicle stimulating hormone (FSH) taught by De Meere by using the teachings of benzyl alcohol regarding preserving, concentration, and solubilizations taught by Buch-Rasmussen and Bornstein." The Examiner further alleges, "The motivation and expected success is provided both by Buch-Rasmussen and Bornstein who teach longer storage of pharmaceutical compositions and antibacterial action using benzyl alcohol."

B. Summary of Applicants' Argument

1. The combination of De Meere in view of Buch-Rasmussen and Bornstein does not establish a *prima facie* case of obviousness for any one of Claims 92-95.
   a. None of the cited art provides any suggestion or motivation to combine.
   b. None of the cited art provides a reasonable expectation of success for achieving a formulation of the claimed invention.
2. Even if the combination of De Meere in view of Buch-Rasmussen and Bornstein does establish a *prima facie* case of obviousness for the present invention as claimed (which Applicants do not concede), evidence from the Applicants' specification rebuts any *prima facie* obviousness.
   a. Evidence from the specification indicates surprising, unexpected, and unpredictable maintenance of stability provided by the combination of FSH and benzyl alcohol in the claimed formulation.
   b. The prior art indicates that there has been a long-felt but unresolved need for stable, preserved formulations of FSH. Stable, preserved formulations are especially needed where extended treatments (twenty-four hours or greater) are required or advised.
3. After all the evidence is given its proper weight, the preponderance of the evidence favors the conclusion that the present invention as claimed is patentable over the combination of De Meere with Buch-Rasmussen and Bornstein.

C. The Rejected Claims

Claims 92-95 are rejected as allegedly obvious. Claim 92 is an independent claim, with Claims 93-95 depending from Claim 92. Claim 92 covers a *formulation* comprising human *FSH* and *benzyl alcohol* in an aqueous diluent.

D. The Law Relating to Obviousness Under 35 U.S.C. § 103(a)

Three criteria must be met to establish a *prima facie* case of obviousness: (1) suggestions or motivation to modify or combine reference teachings, (2) reasonable expectation of success, and (3) the prior art reference must teach or suggest all the claim limitations. MPEP § 2143. "Particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d

1313, 1317 (Fed. Cir. 2000). The rejection "must be based on objective evidence of record." *In re Lee*, 277 F.3d 1338, 1343, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002).

"A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. MPEP § 2414.02 (citing *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)). "It is impermissible . . . to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." *Bausch and Lomb, Inc. v. Barnes-Hind, Inc.*, 796 F.2d 443, 448, 230 U.S.P.Q. 416 (Fed. Cir. 1986) (citing *In re Wesslau*, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965)).

"The [E]xaminer bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. . . . If . . . the [E]xaminer does produce a *prima facie* case, the burden of coming forward with evidence or arguments shifts to the [A]pplicant who may submit additional evidence of nonobviousness." MPEP § 2142.

E. De Meere's Disclosure

The Examiner states that De Meere teaches recombinant FSH and concentrations of FSH that overlap with concentrations claimed in the instant application. The Examiner further states that De Meere does not teach concentrations of benzyl alcohol in an aqueous diluent.

Applicants respectfully disagree that the teachings of De Meere are applicable to the present invention. De Meere teaches that **lyophilized** recombinant FSH can be stabilized by formulating FSH with a dicarboxylic acid salt stabilizer and that an ampoule may contain from 1 to 1000 μg of FSH. De Meere also teaches that a reconstituted injectable preparation can be made from the lyophilisate, which preparation consists essentially of water for injection, the gonadotropin (e.g., FSH), a non-reducing sugar, an anti-absorption agent, and the dicarboxylic acid salt. However, De Meere provides no teaching with respect to stability of the reconstituted preparation. Instead, De Meere exemplifies the stability of lyophilized formulations only, comprising FSH and various dicarboxylic acid salt stabilizers.

De Meere does not teach or suggest the addition of any preservative, including benzyl alcohol, in stabilized FSH formulations. There is no suggestion that a stable recombinant FSH formulation could be produced for multi-use, nor is there any suggestion that benzyl alcohol could be used as a preservative for a multi-use FSH product. Indeed, the prior art teaches that preservatives tend to denature or destabilize protein or induce

aggregation (Brange and Langkjar, *Acta Pharm. Nord* 4:149-158 (1992); Maa and Hsu, *Intl. J. Pharm.* 140:155-168 (1996)) (*see* the instant application page 54, lines 26-30). Surprisingly, benzyl alcohol did not significantly aggregate FSH in the instant application.

In contrast, the instant invention provides a formulation comprising FSH and benzyl alcohol, in which FSH is physically and conformationally stable. Moreover, the instant application provides evidence of maintained stability of FSH reconstituted in a benzyl alcohol diluent. *See* the instant application, Example 13 (mislabeled as second Example 9, corrected through this amendment), for dissociation of the FSH heterodimer as a function of time and temperature.

F. Buch-Rasmussen's Disclosure

The Examiner states that Buch-Rasmussen teaches that aqueous solutions or suspensions of medicaments, such as insulin or growth hormones, are normally provided with a preservative such as benzyl alcohol, and that benzyl alcohol is approved in small amounts for use in parenteral medicaments.

Applicants respectfully disagree that the teachings of Buch-Rasmussen are applicable to the present invention. The invention of Buch-Rasmussen is a polymeric container for aqueous solutions or suspensions of medicaments, especially the monomeric proteins insulin or growth hormone. Buch-Rasmussen teaches that some polymeric containers can be problematic for the storage of aqueous medicaments due to (1) the loss of phenol, benzyl alcohol, and m-cresol from the solutions (see Buch-Rasmussen, column 1, lines 66-67); (2) the loss of water (see Buch-Rasmussen, column 2, lines 17-22); and (3) the lack of transparency, resulting in the inability of the patient to detect changes in the medicament (see Buch-Rasmussen, column 2, lines 23-28). Buch-Rasmussen teaches that some polymeric containers control the loss of preservatives and water. The disclosure explains and exemplifies improvements in containers by measuring physical properties of the polymeric container, loss of m-cresol, water permeability, and light transmission of various polymeric containers (see Buch-Rasmussen, column 6, lines 61-64; column 7, lines 2-3). Buch-Rasmussen does not disclose or teach stability of the protein stored in the polymeric container.

In contrast, the instant invention provides a formulation comprising FSH and benzyl alcohol, in which FSH maintains physical and conformational stability in the formulation. The present application provides data indicating that the stability of FSH is maintained in the formulation. *See* the instant application: Example 6 for particle size of

FSH; Example 7 for thermal denaturation of FSH; and Example 13 for dissociation of the FSH heterodimer as a function of time and temperature.

G. Bornstein's Disclosure

The Examiner states that Bornstein teaches that benzyl alcohol is known as a preservative in pharmaceutical formulations based on its antibacterial action and as a solubilizing agent for certain pharmaceutical compounds, and the disclosed benzyl alcohol concentrations overlap concentrations claimed in the instant application.

Applicants respectfully disagree that the teachings of Bornstein are applicable to the present invention. Bornstein teaches that benzyl alcohol in the concentration range from about 5 mg/mL to about 30 mg/mL can be used to solubilize 2-chloro-2′-deoxyadenosine (2-CdA), a nucleoside, in water, thereby greatly increasing the solubility of the nucleoside. To exemplify the increased solubility of 2-CdA, Bornstein prepared solutions of 2-CdA with varying concentrations of benzyl alcohol and periodically tested the solutions for the amount of 2-CdA. The amount of 2-CdA remaining in solution after 32 days increased as the concentration of benzyl alcohol increased from 0 mg/mL to 30 mg/mL. Hence, Bornstein teaches stability, measured only by solubility, of a nucleoside in varying concentrations of benzyl alcohol, including a 10 mg/mL benzyl alcohol solution.

Through the solubility experiment, Bornstein teaches that a "certain pharmaceutical compound," 2-CdA, can be solubilized by the addition of benzyl alcohol. Bornstein does not teach solubility of all pharmaceutical compounds. Bornstein does not teach that increased solubility of a simple nucleoside in benzyl alcohol is predictive of maintained physical and conformational stability of a complex heterodimeric protein in a formulation comprising FSH and benzyl alcohol.

H. No *Prima Facie* Case of Obviousness

Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness in combining De Meere, Buch-Rasmussen, and Bornstein. First, none of the cited art suggests or motivates one of ordinary skill in the art to combine the prior art in a manner that the Examiner has combined them. Second, there is no reasonable expectation of success in achieving the claimed invention by combining the cited art.

None of the cited art teaches, suggests, or motivates one of ordinary skill in the art to combine De Meere with Buch-Rasmussen and Bornstein. De Meere suggests and teaches the use of a dicarboxylic acid salt to obtain a stable lyophilized formulation of FSH. De Meere does not suggest or motivate one to use benzyl alcohol or any other preservative to obtain a stable solution formulation of FSH.

Nor does Buch-Rasmussen or Bornstein suggest or motivate one to use benzyl alcohol in a formulation comprising FSH. Buch-Rasmussen teaches that the loss of m-cresol, phenol, benzyl alcohol, and water from medicaments, such as insulin and growth hormone, can be controlled by the use of certain containers (glass and some polymers), allowing longer storage. Bornstein teaches that benzyl alcohol is useful as a preservative and solubilizing agent for certain pharmaceutical compounds such as the nucleoside 2-CdA. Neither reference suggests or motivates one to use benzyl alcohol to stabilize a non-covalently-bonded heterodimeric protein like FSH in a formulation. Although both Buch-Rasmussen and Bornstein comment that benzyl alcohol can be used with "certain" pharmaceuticals, neither suggests which pharmaceuticals will tolerate benzyl alcohol and which will not.

A person of ordinary skill in the art would understand that physical and conformational stability of a non-covalently bonded heterodimer like FSH is not the same as "longer storage" of simple mononucleosides like 2-CdA or simple monomeric proteins like insulin and growth hormone. These molecules are significantly different in physical and conformational structure from each other and from FSH. Stability of the non-covalently bonded heterodimer is not predictable based on the stability and/or solubility of a covalently bonded nucleoside or monomeric protein. The Examiner fails to cite any objective evidence to indicate the reason that a person of ordinary skill in the art would be motivated to combine De Meere, Buch-Rasmussen, and Bornstein, despite the fact that the structures of the molecules vary so significantly. The mere fact that the cited art recites "pharmaceutical compositions" does not create a reasonable expectation that all pharmaceutical compositions will be stabilized by the addition of benzyl alcohol.

For the preceding reasons, the Applicants assert that Claims 92-95 are not *prima facie* obvious because of De Meere in view of Buch-Rasmussen and Bornstein. Applicants respectfully request the Examiner to remove the rejection of Claims 92-95 under 35 U.S.C. § 103(a), and to advance the application to issue.

I. Rebuttal Evidence

Applicants believe that they have convincingly demonstrated that Claims 92-95 are not *prima facie* obvious because of De Meere in view of Buch-Rasmussen and Bornstein. Nevertheless, to advance prosecution of this application in case the Examiner does not accept the Applicants' arguments on *prima facie* obviousness, Applicants now provide rebuttal evidence from the instant application.

The data from Table VI. in Example 6 show the effect of preservatives on physical stability of FSH. Although preservatives tend to denature or destabilize protein or induce aggregation (Brange and Langkjar, *Acta Pharm. Nord* 4:149-158 (1992); Maa and Hsu, *Intl. J. Pharm.* 140:155-168 (1996)) (*see* the instant application page 54, lines 26-30), surprisingly, benzyl alcohol did not significantly aggregate uFSH under the conditions tested. The formulation containing benzyl alcohol maintained stability similar to a non-preserved formulation. Thus, the addition of benzyl alcohol did not destabilize the protein as would have been suggested by the prior art.

Preservative	Preservative Concentration (mg/ml)	Small Particles (~ 5.7 nm)	Large Particles (~ 200 nm)
None	0	>99 %	< 1 %
Benzyl alcohol	10	>99 %	< 1 %

The data from Table VII. in Example 7 indicate the effect of the addition of preservatives to uFSH formulations on the thermal denaturation of the protein. High melting temperature (T_m) of protein unfolding transitions indicates high protein stability. The addition of benzyl alcohol to an FSH solution shows only marginal effect on T_m.

Solution conditions	T_m (°C)
uFSH in PBS at pH 7.4	77.3
10 mg/mL benzyl alcohol	73.5

The data from Table XIII. in Example 13 show the formulation stability of a recombinant FSH variant in phosphate buffered saline with and without preservative. Samples were stored at various temperatures for up to three months, and the % dimer was periodically measured by size exclusion chromatography. These data indicate that there is minimal dissociation of an FSH solution containing benzyl alcohol after three months at room temperature or below. Again, these data indicate maintained stability despite the addition of the expected protein destabilizing agent, benzyl alcohol.

	% Dimer at 1 month			% Dimer at 3 months		
Sample	4°C	22°C	37°C	4°C	22°C	37°C
20 µg/mL FSH in PBS	100	100	88.9	100	100	77.3
20 µg/mL FSH in PBS 10 mg/mL benzyl alcohol	100	100	89.1	100	100	57.1
50 µg/mL FSH in PBS	100	100	100	100	100	81.1
50 µg/mL FSH in PBS 10 mg/mL benzyl alcohol	100	100	87	100	100	61.0

J. Rebuttal Argument and Conclusion

The physical and conformational stability of the formulation disclosed in the instant application are completely surprising, unexpected, and unpredictable when compared to the combination of De Meere in view of Buch-Rasmussen and Bornstein. "Obviousness cannot be predicated on what is unknown." *In re Naylor*, 369 F.2d 765, 768, 152 U.S.P.Q. 106 (C.C.P.A. 1967).

The cited art does not suggest the present invention. De Meere requires the addition of a dicarboxylic acid salt stabilizer to stabilize lyophilized FSH. Buch-Rasmussen discloses decreased loss of benzyl alcohol from certain pharmaceutical formulations (insulin and growth hormone) by using specific polymeric containers. Bornstein discloses the use of benzyl alcohol to solubilize certain pharmaceutical formulations (2-CdA). None of the art, even when combined, suggests or teaches maintained stability of FSH solutions containing benzyl alcohol.

In contrast, the data disclosed in the present invention clearly demonstrates that the physical and conformational stability of FSH is maintained in solution. Notwithstanding prior art that indicates "[t]here is substantial evidence in the literature indicating that heterodimers can dissociate under physiological or acidic conditions (Ryan, R.J., et al., *Recent Progr. Hormone Res.* 26:105-137; 1970, Strickland, TW and Puett, D, *J. Biol. Chem.* 257:2954-2960; 1982, Reichert LE and Ramsey RB, *J. Biol. Chem.* 250:3034-

3040; 1975)" (*see* the instant application page 4, lines 7-13), and since "[t]he alpha and beta subunits [of FSH] bind non-covalently . . . ,the binding was thought to be more susceptible to protein destabilization agents" (*see* the instant application page 3, lines 14-16), the instant application exemplifies that a solution formulation of FSH and benzyl alcohol maintains stability over an extended period of time. This maintained stability could not be predicted from Buch-Rasmussen or Bornstein, which contained only monomeric proteins and a mononucleoside, or a combination of De Meere in view of Buch-Rasmussen and Bornstein.

Because the structures of the active pharmaceutical ingredients of Buch-Rasmussen and Bornstein are so physically, chemically, and conformationally different from the heterodimer of the instant application, the Applicants assert that the formulation of the instant application yields surprising, unexpected, and unpredictable maintained stability of reconstituted FSH compositions.

Furthermore, there has been a long-felt but unresolved need for stable, preserved formulations of FSH, which are especially needed where extended treatments (twenty-four hours or greater) are required or advised. Non-preserved or unstable formulations require reconstitution of the sample before each use and disposal of any unused liquid. The instant invention meets the long-felt need by providing stable, preserved formulations that are advantageous since the reconstituted sample can be used multiple times.

In conclusion, the Applicants respectfully assert that Claims 92-95 are not *prima facie* obvious in light of a combination of De Meere, Buch-Rasmussen, and Bornstein. Applicants further maintain that the definitive evidence of stability of the formulation of the instant application is surprising, unexpected, and unpredictable in light of a combination of De Meere, Buch-Rasmussen, and Bornstein, and has resolved a long-felt need in the field. Thus, the claimed invention is not obvious over the cited art.

Finally, Applicants submit that when all the evidence is given its proper weight, the preponderance of the evidence only permits a conclusion that the claimed invention is patentable over the combination of De Meere in view of Buch-Rasmussen and Bornstein. Applicants respectfully request that the Examiner remove the rejection of Claims 92-95 under 35 U.S.C. § 103(a) as obvious over De Meere in view of Buch-Rasmussen and Bornstein, and that the application be advanced to issue.

III. Rejection of Claims 96-103 under 35 U.S.C. § 103(a)

A. The Rejections

The Examiner rejected Claims 96-103 under 35 U.S.C. § 103(a) as unpatentable over De Meere, *et al.* (US Patent No. 5,384,132; "De Meere") in view of Buch-Rasmussen, *et al.* (US Patent No. 5,945,187; "Buch-Rasmussen") and Bornstein, *et al.* (US Patent No. 5,681,822; "Bornstein") and further in view of Carey, *et al.* (US Patent No. 4,746,508; "Carey"). The Examiner alleges that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of De Meere, *et al.*, Buch-Rasmussen, *et al.*, and Bornstein, *et al.*, and use the teachings of Carey, *et al.*" The Examiner further alleges, "The motivation and expected success is provided by the use of sodium phosphate, which is taught as a physiologically acceptable carrier and offers buffering capacity that maintains the pH."

B. Summary of Applicants' Argument

1. The combination of De Meere in view of Buch-Rasmussen, Bornstein, and Carey does not establish a *prima facie* case of obviousness for any one of Claims 96-103.
   a. None of the cited art provides any suggestion or motivation to combine.
   b. None of the cited art provides a reasonable expectation of success for achieving a formulation of the claimed invention.
2. Even if the combination of De Meere in view of Buch-Rasmussen, Bornstein, and Carey does establish a *prima facie* case of obviousness for the present invention as claimed (which Applicants do not concede), evidence from the Applicants' specification rebuts any *prima facie* obviousness.
   a. Evidence from the specification indicates surprising, unexpected, and unpredictable maintenance of stability provided by the combination of FSH and benzyl alcohol in the claimed formulation.
   b. The prior art indicates that there has been a long-felt but unresolved need for stable, preserved formulations of FSH. Stable, preserved formulations are especially needed where extended treatments (twenty-four hours or greater) are required or advised.

3. After all the evidence is given its proper weight, the preponderance of the evidence favors the conclusion that the present invention as claimed is patentable over the combination of De Meere with Buch-Rasmussen, Bornstein, and Carey.

C. The Rejected Claims

Claims 96-103 are rejected as allegedly obvious. Claims 96-103 are dependent claims, each of which ultimately depend from independent Claim 92. Claims 96-103 cover *formulation* comprising human *FSH* and *benzyl alcohol* in an aqueous diluent, further comprising *sodium phosphate*.

D. The Law Relating to Obviousness Under 35 U.S.C. § 103(a)

Claims 96-103 are rejected under 35 U.S.C. § 103(a), just as Claims 92-95 are. Thus, the same law applies. *See* section II.D., *supra*.

E. The Disclosures of De Meere, Buch-Rasmussen, and Bornstein

The disclosures of De Meere, Buch-Rasmussen, and Bornstein are discussed and compared to the instant application in a previous section of this response. *See* sections II.E., F., and G.

F. Carey's Disclosure

The Examiner states that Carey, *et al.*, teach the administration of follicle stimulating hormone and the use of sodium phosphate as a physiologically acceptable carrier.

Applicants respectfully disagree that the teachings of Carey are applicable to the present invention. Carey teaches methods and compositions for administering a drug that increases drug permeability of a body surface across which the drug is administered, thereby avoiding problems associated with other modes of drug administration such as injection. The compositions comprise a drug and a water-soluble steroid adjuvant. The methods claim administration of the composition to a mucosal surface for absorption. FSH is disclosed in a list of suitable peptides, which may be administered accordingly. Sodium phosphate is disclosed as a physiologically acceptable carrier for intranasal or conjunctival delivery of the composition.

Carey does not teach or suggest that the disclosed compositions are useful without the steroid adjuvant. Carey does not address or demonstrate any of the following:

(1) stability of the composition, with or without the steroid adjuvant; (2) multi-use of the composition; or (3) use of the composition as a parenteral drug. Conversely, the instant application specifically provides a stable FSH formulation for multi-use which can be administered by injection.

G. No *Prima Facie* Case of Obviousness

Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness in combining De Meere, Buch-Rasmussen, Bornstein, and Carey. The arguments stated in section II.H. of this response, regarding the rejection of Claims 92-95, further apply to the rejections of Claims 96-103. The addition of the Carey reference does not advance the Examiner's case for prima facie obviousness. Even with the inclusion of Carey, none of the cited art suggests or motivates one of ordinary skill in the art to combine the prior art in a manner that the Examiner has combined them. Second, there is no reasonable expectation of success in achieving the claimed invention by combining the cited art.

There is no teaching, suggestion, or motivation in De Meere, Buch-Rasmussen, Bornstein, or Carey to combine these four patents to yield a stable formulation comprising FSH, benzyl alcohol, and sodium phosphate. As stated previously, the compounds disclosed in the referenced patents are so different in physical and conformational structure from each other and from FSH that maintained stability of the non-covalently bonded heterodimer is not predictable. The Examiner provides no substantive explanation of why the skilled artisan would have chosen to combine these patents, without the benefit of hindsight reconstruction.

Moreover, even if combined as the Examiner suggests, the composition would contain additional components which the present invention does not contain. For example, Carey requires that the composition contain a steroid adjuvant. The instant application does not require the addition of a steroid adjuvant; in fact, no steroid is disclosed or claimed anywhere in the instant application. "It is impermissible . . . to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." *Bausch and Lomb, Inc. v. Barnes-Hind, Inc.*, 796 F.2d 443, 448, 230 U.S.P.Q. 416 (Fed. Cir. 1986). Combining De Meere, Buch-Rasmussen, Bornstein, and Carey would yield a formulation with additional components (e.g., a steroid adjuvant) which cannot be selective removed from the formulation to make a case of prima facie obviousness. The prior art must

be considered as a whole. The Examiner provides no evidence supporting deletion of the required steroid adjuvant from the combined formulation.

Furthermore, as the pharmaceutical field is unpredictable, there is no reasonable expectation of success by combining the referenced art. The Examiner has selectively chosen FSH from De Meere and Carey, benzyl alcohol from Buch-Rasmussen and Bornstein, and sodium phosphate from Carey. Yet, there is no reasonable expectation that the benzyl alcohol of Buch-Rasmussen and Bornstein, *neither of which disclosed FSH or any other heterodimeric protein*, when combined with FSH and sodium phosphate, would provide a stable formulation for multi-use. Nor is there a reasonable expectation of success that the composition of Carey will be stable upon removal of the steroid adjuvant or that this altered composition could be used as a parenteral formulation.

For the preceding reasons, the Applicants assert that Claims 96-103 are not *prima facie* obvious because of De Meere in view of Buch-Rasmussen, Bornstein, and Carey. Applicants respectfully request the Examiner to remove the rejection of Claims 96-103 under 35 U.S.C. § 103(a), and to advance the application to issue.

H. Rebuttal Evidence

Applicants believe that they have convincingly demonstrated that Claims 96-103 are not *prima facie* obvious because of De Meere in view of Buch-Rasmussen, Bornstein, and Carey. Nevertheless, to advance prosecution of this application in case the Examiner does not accept the Applicants' arguments on *prima facie* obviousness, Applicants have provided rebuttal evidence from the instant application. The evidence rebutting the rejection of Claims 92-95, shown in section II. I., *supra*, of this response, also applies to the rejection of Claims 96-103.

IV. Affirmation of Common Ownership under 35 U.S.C. § 103(c)

The Examiner notes that the application names joint inventors. The Applicants affirm the Examiner's presumption that the subject matter of the various claims was commonly owned at the time of invention.

V. Conclusions

In view of the remarks and amendments provided herein, the Applicants respectfully submit that the objection and rejections have been overcome. Reconsideration and withdrawal of each are therefore requested.

The Applicants urge the Examiner to call the Applicants' agent at (317) 433-3422 if a telephone conversation or office interview would be helpful in expediting the prosecution of this case.

Respectfully submitted,

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